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Bezeichnung: Use of vasopeptidase inhibitors in the treatment of metabolic diseases, nephropathy and AGE associated diseases

IPC: A 61 K 31/55

Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Patentanmeldung.

München, den 25. November 2002
Deutsches Patent- und Markenamt
Der Präsident
Im Auftrag

Weihmayr

A 9161
06/00
EDV-L

Description

Use of Vasopeptidase Inhibitors in the Treatment of Metabolic Diseases, Nephropathy and AGE associated diseases

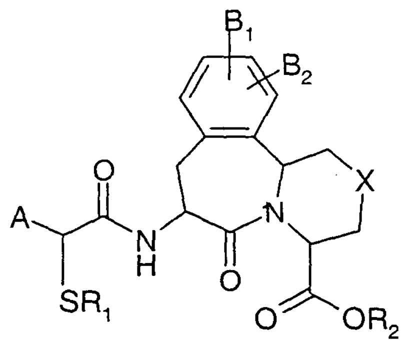
Angiotensin-Converting Enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor which also stimulates aldosterone secretion by the adrenal cortex. ACE inhibition prevents both the conversion of Angiotensin I to angiotensin II and the metabolism of bradykinin, resulting in decreased circulating angiotensin II, aldosterone and increased circulating bradykinin concentrations. In addition to these neurohormonal changes, decreases in peripheral resistance and blood pressure are observed, particularly in individuals with high circulating renin. Other pharmacological effects associated with ACE inhibition include regression of left ventricular hypertrophy, improvement in the clinical signs of heart failure, and reduction in mortality in patients with congestive heart failure (CHF) or left ventricular dysfunction after myocardial infarction.

Neutral endopeptidase (NEP) is an enzyme responsible for the metabolism of atrial natriuretic peptide (ANP). Inhibition of NEP results in increased ANP concentrations, which in turn leads to natriuresis, diuresis and decreases in intravascular volume, venous return and blood pressure. ANP is released by atrial myocytes in response to atrial stretch or increased intravascular volume. Elevated plasma concentrations of ANP have been demonstrated as a potential compensatory mechanism in various disease states, including congestive heart failure, renal failure, essential hypertension and cirrhosis.

The secretion of ANP by atrial myocytes causes vasodilation, diuresis, natriuresis, and the inhibition of renin release and aldosterone secretion. In contrast, angiotensin II results in vasoconstriction, sodium and water reabsorption, and aldosterone production. These two hormonal systems interact in a reciprocal or counterbalancing

manner to maintain normal physiologic vascular and hemodynamic responses. U.S. patent 5,430,145, European patent EP 481522 and WO patent application PCT/EP 02/03668 disclose tricyclic mercaptoacetylamide derivatives of the formula (I) useful as ACE and NEP inhibitors, i.e. for the treatment and/or prevention of heart failure and hypertension.

This invention is directed to the use of a compound of formula (I)



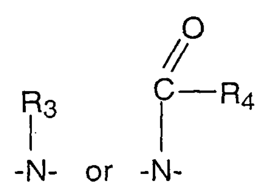
wherein

A = H, C_1-C_8-alkyl, $CH_2OCH_2CH_2OCH_3$, -(C_1-C_4-alkyl)-aryl;

R_1 is hydrogen, -$CH_2OC(O)C(CH_3)_3$, or an acyl group;

R_2 is hydrogen; -CH_2O-$C(O)C(CH_3)_3$; a C_1-C_4-alkyl; aryl, -(C_1-C_4-alkyl)-aryl; or diphenylmethyl;

X is –$(CH_2)_n$ wherein n is an integer 0 or 1, -S- , –O- ,

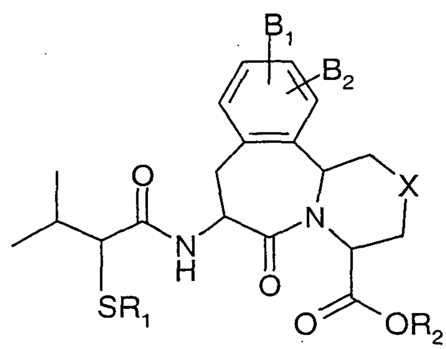


wherein R_3 is hydrogen, a C_1-C_4-alkyl, aryl or aryl-(C_1-C_4-alkyl) and R_4 is –CF_3, C_1-C_{10}-alkyl, aryl, or aryl-(C_1-C_4-alkyl);

B_1 and B_2 are each independently hydrogen, hydroxy, -OR_5, wherein R_5 is C_1-C_4-alkyl, aryl, or -(C_1-C_4-alkyl)-aryl or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbon atoms to form a benzene ring or methylenedioxy,

for the treatment and/or prophylaxis of nephropathy in diabetic or non-diabetic patients, including diabetic and non-diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndome, hypertensive nephrosclerosis, microalbuminuria or end stage renal disease, or to a method of treatment and/or prophylaxis of insulin resistence or of metabolic diseases associated with advanced glycation end-products, diabetic complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, myocardial infarction and/or diabetic cardiomyopathy, or to a method of treatment and/or prophylaxis of atherosclerosis or endothelial dysfunction.

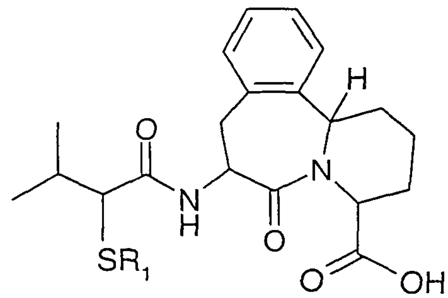
In one embodiment, the present invention provides the above uses of a compound of a formula (I) characterized by a compound of the formula (II)



(II)

wherein R_1 is acetyl. In another embodiment, the present invention provides the above uses of a compound of the formula (II) wherein R_1 is hydrogen. In a further embodiment, the present invention provides the above uses of a compound of the formula (II) wherein R_2 is hydrogen. In a further embodiment, the present invention provides the above uses of a compound of the formula (II) wherein B_1 and/or B_2 are hydrogen. In yet a further embodiment, the present invention provides the above uses of a compound of the formula (II) wherein X is $-CH_2$.

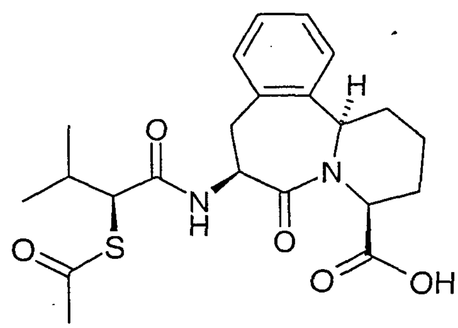
In a further embodiment, the present invention provides the above uses of a compound of the formula (I) characterized by a compound of the formula (II-A):



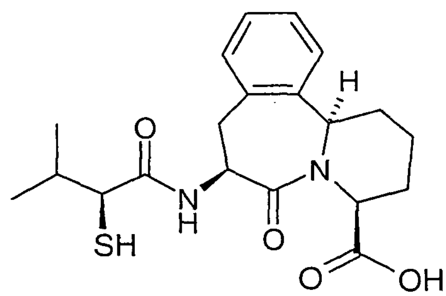
(II-A)

wherein R_1 is acetyl or hydrogen.

The structure of preferred compounds of the formulae (II-A) are of the formula (II-B), also referred to as compound (II-B) or cpd. (II-B), and of the formala (II-C) below:

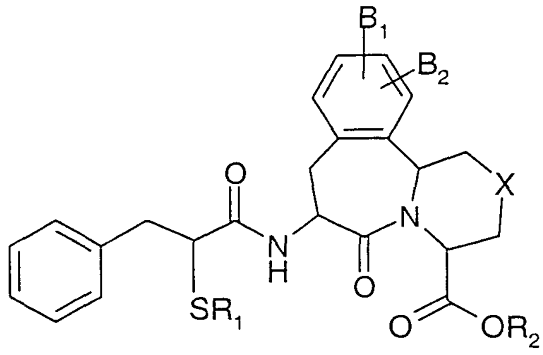


(II-B)



(II-C)

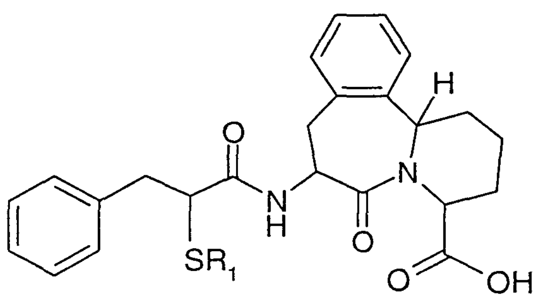
In a further embodiment, the present invention provides the above uses of a compound of the formula (I) characterized by a compound of the formula (III)



(III)

wherein R_1 is acetyl. In another embodiment, the present invention provides the above uses of a compound of the formula (III) wherein R_1 is hydrogen. In a further embodiment, the present invention provides the above uses of a compound of the formula (III) wherein R_2 is hydrogen. In a further embodiment, the present invention provides the above uses of a compound of the formula (III) wherein B_1 and/or B_2 are hydrogen. In yet a further embodiment, the present invention provides the above uses of a compound of the formula (III) wherein X is $-CH_2$.

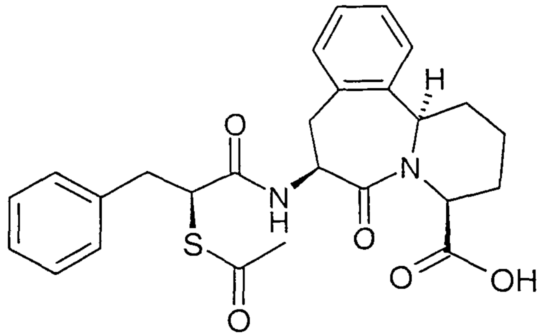
In a further embodiment, the present invention provides the above uses of a compound of the formula (I) characterized by a compound of the formula (III-A):



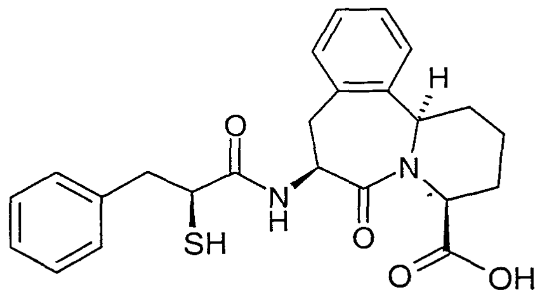
(III-A)

wherein R_1 is acetyl or hydrogen.

The structure of preferred compounds of the formulae (III-A) are of the formula (III-B) and (III-C) below:



(III-B)



(III-C)

As used herein, the term 'C_1-C_4-alkyl' refers to a saturated straight or branched monovalent hydrocarbon chain of one, two, three or four carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, and the like groups. The term 'C_1-C_{10}-alkyl' refers to a saturated straight or branched monovalent hydrocarbon chain of one to ten carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like groups.

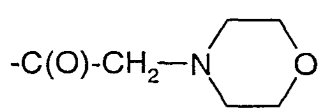
As used herein, 'C_1-C_4-alkoxy' refers to a monovalent substitutent which consists of a straight or branched alkyl chain having from 1 to 4 carbon atoms linked through an ether oxygen atom and having its free valence bond from the ether oxygen, and includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy and the like groups.

As used herein, 'aryl' refers to a phenyl or naphthyl group unsubstituted or substituted with from one to three substituents selected from the group consisting of methylenedioxy, hydroxy, C_1-C_4-alkoxy, fluoro and chloro. Included within the scope

of the term '-(C_1-C_4-alkyl)-aryl' are phenylmethyl (benzyl), phenylethyl, p-methoxybenzyl, p-fluorobenzyl and p-chlorobenzyl.
As used herein, 'heterocycle' means any closed-ring moiety in which one or more of the atoms of the ring are an element other than carbon and includes, but is not limited to the following: piperidinyl, pyridinyl, isoxazolyl, tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperazinyl, benzimidazolyl, thiazolyl, thienyl, furanyl, indolyl, 1,3-benzodioxolyl, tetahydropyranyl, imidazolyl, tetrahydrothienyl, pyranyl, dioxanyl, pyrrolyl, pyrimidinyl, pyrazinyl, thiazinyl, oxazolyl, purinyl, quinolinyl and isoquinolinyl.

As used herein, 'halogen' or 'Hal' refers to a member of the family of fluorine, chlorine, bromine or iodine.

As used herein, 'acyl group' refers to aliphatic and aromatic acyl groups and those derived from heterocyclic compounds. For example, the acyl group may be a lower or (C_1-C_4)alkanoyl group such as formyl or acetyl, an aroyl group such as benzoyl or a heterocyclic acyl group comprising one or more of the heteroatoms O, N and S, such as the group



As used herein, 'stereoisomer' is a general term used for all isomers of individual molecules that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers), geometric (cis/trans or E/Z) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers).

As used herein, 'R' and 'S' are used as commonly used in organic chemistry to denote specific configuration of a chiral center. The term 'R' (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term 'S' (sinister) refers to that configuration of a chiral center with a

counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon sequence rules wherein prioritization is first based on atomic number (in order of decreasing atomic number). A listing and discussion of priorities is contained in Stereochemistry of Organic Compounds, Ernest L. Eliel, Samuel H. Wilen and Lewis N. Mander, editors, Wiley-Interscience, John Wiley & Sons, Inc., New York, 1994.

In addition to the (R)-(S) system, the older D-L system may also be used herein to denote absolute configuration, especially with reference to amino acids. In this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix 'D' is used to represent the absolute configuration of the isomer in which the functional (determing) group is on the right side of the carbon at the chiral center and 'L', that of the isomer in which it is on the left.

As used herein, 'treat' or 'treating' means any treatment, including but not limited to, alleviating symptoms, eliminating the causation of the symptoms either on a temporary or permanent basis, or to preventing or slowing the appearance of symptoms and progression of the named disease, disorder or condition.

As described herein, the term 'patient' refers to a warm blooded animal such as a mammal which is afflicted with a particular disease, disorder or condition. It is explicitly understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans are examples of animals within the scope of the meaning of the term.

As used herein, the term 'pharmaceutically acceptable salt' is intended to apply to any salt, whether previously known or future discovered, that is used by one skilled in the art that is a non-toxic organic or inorganic addition salt which is suitable for use as a pharmaceutical. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium or magnesium hydroxides; ammonia and aliphatic, cyclic or aromatic amines such as methylamine, dimethylamine, triethylamine, diethylamine, isopropyldiethylamine, pyridine and picoline. Illustrative acids which form suitable salts include inorganic acids such as, for example, hydrochloric, hydrobromic, sulfuric, phosphoric and like

acids, and organic carboxylic acids such as, for example, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, mandelic and like acids, and organic sulfonic acids such as methanesulfonic and p-toluenesulfonic acids.

As used herein, 'pharmaceutical carrier' refers to known pharmaceutical excipients useful in formulating pharmaceutically active compounds for administration, and which are substantially nontoxic and nonsensitizing under conditions of use. The exact proportion of these excipients is determined by the solubility and chemical properties of the active compound, the chosen route of administration as well as standard pharmaceutical practice.

The compositions of the compound of the formula (I) of this invention may be administered to a subject in need of treatment by a variety of conventional routes of administration, including orally, topically, parenterally, e.g., intravenously, subcutaneously or intramedullary. Further, the active compositions of this invention may be administered intranasally, as a rectal suppository or using a "flash" formulation, i.e., allowing the medication to dissolve in the mouth without the need to use water.

The active compositions of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, vehicles or diluents, in either single or multiple doses. Suitable pharmaceutical carriers, vehicles and diluents include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the active compositions of this invention and the pharmaceutically acceptable carriers, vehicles or diluents are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic

acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of the active compositions of this invention in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solutions may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Generally, a composition of this invention is administered orally, parenterally (e.g., intravenous, intramuscular, subcutaneous or intramedullary), or topical. For intranasal administration or administration by inhalation, one or more compound of this inventions of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol , the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a

suitable powder base such as lactose or starch. For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995).

NEPHROPATHY:

Nephropathy is a chronic disease that is defined as abnormality in the excretion of urinary albumin in diabetic or non-diabetic patients. Urinary albumin excretion rates are less than or equal to 40 mg/24 Hours in healthy humans. The clinical stages of nephropathy are microalbuminuria, clinical nephropathy (albuminuria) and end stage renal disease (ESRD).

A common form of nephropathy is diabetic nephropathy. Diabetic nephropathy develops in 35 to 40% of patients with type 1 diabetes mellitus and in 10 to 60% of patients with type 2 diabetes mellitus depending upon the ethnic pool being studied and is the most common cause of end-stage renal disease in the United States. It is accepted that diabetic nephropathy is the result of hyperglycemia, whether alone or in combination with other factors, such as hypertension and genetic susceptibility to kidney disease. Appropriate antihypertensive therapy has been shown to significantly reduce renal and possibly cardiovascular mortality in proteinuric type 1 diabetes mellitus patients, as well as retard the rate of decline of glomerular filtration rate in some patients with impaired renal function (Lewis et al., N. Engl. J. Med. 1993, 329, 1456-1462). Thus, the standard care for patients with diabetic nephropathy is intensive glycemic control and normalization of the blood pressure using primarily angiotensin converting enzyme (ACE) inhibitors such as ramipril.

Some vasopeptidase inhibitors have shown to exhibit a greater nephroprotective effect than ACE inhibitors alone (Molinaro et al., Curr. Opin. Pharmacol. 2002, 2,

131-141), such as omapatrilat as one of the earliest developed and the most extensively evaluated vasopeptidase inhibitors. Chen et al. (Hypertension 2001, 38, 187-191) defined the renal action of acute treatment with omapatrilat and ACE inhibitor fosinoprilat, wherein omapatrilat had a greater natriuretic response than the ACE inhibitor. In another study, vasopeptidase inhibitor CGS 30440 (Novartis, Switzerland) had a greater renal protective effect than ACE inhibitor benazepril (Cohen et al., J. Cardiovasc. Pharmacol. 1998, 32, 87-95).

It has now been shown that vasopeptidase inhibitors of the formula (I) have a superior nephroprotective effect in albumin excretion rate and is therefore useful for the treatment and/or prevention of nephropathy in diabetic and non-diabetic patients, including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndome, hypertensive nephrosclerosis, microalbuminuria and end stage renal disease.

The effect of compound (II-B) is 6-8fold higher than observed with ACE inhibitor ramipril.

Example 1: Diminishing proteinuria by treatment with a compound of the formula (II-B)

The protein and creatinin excretion in the urin of male ZDF Rats (ZDF Gmi fa/fa) and heterocygotic control animals (ZDF Gmi -/?) of 10, 17, 27 and 37 weeks age was determined. In further groups diabetic rats were chronically given either ramipril (1 mg/kg/day, drinking water) or a compound of the formula (II-B) (30 mg/kg/day, feeded) over a period from 10 to 37 weeks. The animals were sacrificied after 37 weeks, and their kidney examined histologically.

Table 1: Urinary excretion of albumin and creatinin in obese, lean, ramipril treated and rats treated with a compound of the formula (II-B)

	Albumin	Albumin/Creatinin
Urin excreta	mg/kg/h	mg/mmol

Weeks	0	7	17	27	0	7	17	27
Group 1 Obese								
Mean	0,35	1,78	9,24	14,23	55,27	404,78	975,60	1543,25
s	0,24	1,09	6,70	7,69	41,58	349,65	714,38	819,04
SEM	0,06	0,28	2,02	2,32	10,74	90,28	215,40	246,95
N	15	15	11	11	15	15	11	11
Gruppe 2 Lean								
Mean	0,121	0,090	0,070	0,079	12,828	9,573	5,754	7,313
s	0,041	0,069	0,033	0,051	4,206	6,010	2,772	4,541
SEM	0,009	0,015	0,008	0,014	0,940	1,344	0,693	1,260
N	20	20	16	13	20	20	16	13
t-Test	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
Gruppe 4 Ramipril								
Mean	0,24	1,36	6,26	10,11	37,31	207,35	694,20	1077,88
s	0,12	1,28	4,71	7,20	17,20	198,42	510,20	742,86
SEM	0,03	0,33	1,42	2,17	4,44	51,23	153,83	223,98
N	15	15	11	11	15	15	11	11
t-Test	0,122	0,338	0,242	0,209	0,133	0,067	0,300	0,178
Gruppe 7 cpd. (II-B)								
Mean	0,27	0,09	0,41	1,39	48,56	14,30	44,63	152,71
s	0,18	0,04	0,18	1,67	28,69	5,38	16,47	174,93
SEM	0,05	0,01	0,05	0,50	7,41	1,39	4,97	52,74
N	15	15	11	11	15	15	11	11
t-Test	0,293	0,000	0,000	0,000	0,611	0,000	0,000	0,000

Histological results:

In the attached tables a summary of the findings on the kidneys after a treatment period of 6 month is listed.

The examined groups were:

C1:	Control	lean ZDF rats	
C2:	Control	fat ZDF rats	
D1:	Ramipril	fat ZDF rats	1.0 mg/kg
D4:	cpd. (II-B)	fat ZDF rats	30 mg/kg

Histopathological findings noted were:

- Armanni-Ebstein cells	in renal tubles indicating a diabetic metabolic state.
- Glomerulosclerosis	indicating chronic kidney damage due to a diabetic metabolic state.
- Atrophy: tubule	common spontaneous degenerative lesion in kidneys.
- Casts: tubule	common spontaneous lesion in kidneys.
- Dilatation: pelvis	common spontaneous lesion in kidneys. considered to be an inherited developmental anomaly.

Armanni-Ebstein cells were not present in lean ZDF control rats but in every group of treated fat ZDF rat.

Glomerulosclerosis was not found in lean ZDF control rat and was also not present in animals treated with compound (II-B). Correspondingly, degenerative lesions, atrophy of tubles and tubular casts were found in low incidences in these animals.

Compared to fat ZDF controls in Ramipril or MDL 100.240 treated rats no differences in the incidence of glomerulosclerosis or associated degenerative lesions was present.
These results indicate that treatment with compound (II-B) may prevent the development of "diabetic" glomerulosclerosis and associated degenerative lesions. The lesions in the fat ZDF control rats were of rather low severity.

In addition, a high incidence of pelvic dilatation was noted in animals treated with

compound (II-B).

EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

K0 = Terminal sacrifice group

Table 2: Histologic findings:				
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX Necropsy status: TERMINAL SACRIFICE GROUP (KO)				
SEX	Males			
Dose Group NO. ANIMALS PER DOSE GROUP	C1 12	C2 6	D1 9	D4 9
Kidneys No. Examined	12	6	9	8
- Armanni-Ebstein cells	-	6	7	8
- Glomerulosclerosis	-	6	6	1
- Atrophy: renal tubule	-	6	9	2
- Casts: renal tubule	1	6	8	3
- Dilatation: pelvis	3	2	5	7

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX Necropsy Status: TERMINAL SARCRIFICE GROUP (KO)				
SEX	Males			
Dose Group NO. ANIMALS PER DOSE GROUP	C1 12	C2 6	D1 9	D4 9

Kidneys No. Examined	12	6	9	8
- Armanni-Ebstein cells GRADE 1	-	2	1	-
GRADE 2	-	3	6	5
GRADE 3	-	1	-	3
TOTAL AFFECTED	-	6	7	8
MEAN SEVERITY	-	1.8	1.9	2.4
- Glomerulosclerosis GRADE 1	-	1	-	1
GRADE 2	-	3	4	-
GRADE 3	-	2	2	1
TOTAL AFFECTED	-	6	6	1
MEAN SEVERITY	-	2.2	2.3	1.0
- Atrophy: renal tubule GRADE 1	-	2	4	1
GRADE 2	-	2	4	-
GRADE 3	-	1	1	1
GRADE 4	-	1	-	-
TOTAL AFFECTED	-	6	9	2
MEAN SEVERITY	-	2.2	1.7	2.0
Casts: renal tubule GRADE 1	1	1	1	2
GRADE 2	-	4	7	1
GRADE 3	-	1	-	-
TOTAL AFFECTED	1	6	8	3
MEAN SEVERITY	1.0	2.0	1.9	1.3
Dilatation: pelvis GRADE 2	3	-	1	1
GRADE 3	-	1	2	5

GRADE 4	-	1	2	1
TOTAL AFFECTED	3	2	5	7
MEAN SEVERITY	2.0	3.5	3.2	3.0

Table 3: Urinary excretion of albumin and creatinin in Zucker Diabetic Fatty (ZDF) rats, ramipril treated and rats treated with a compound of the formula (II-B) starting at an animal age of 6 month. ZDF rats are a model for Type II diabetis.

	Albumin/Creatinin mg/mmol		
	Basal	.6 weeks tretament	12 weeks treatment
Placebo ZDF rats			
mean	1330,99	1068,25	1193,47
s	797,55	778,81	633,10
SEM	230,23	224,82	182,76
N	12	12	12
Cpd. (II-B) ZDF rats			
Mean	1330,99	135,08	100,86
S	797,55	40,28	59,27
SEM	230,23	11,63	17,11
N	12	12	12
Ramipril ZDF rats			
Mean	1330,99	1249,59	841,69
S	797,55	1036,03	1124,24
SEM	230,23	299,07	324,54
N	12	12	12

Example 2:

The albumin and creatinin excretion in Goto-Kakizaki (GK) rats was determined. GK rats are a model for Type II diabetis. One group was left untreated, one was treated with the ACE/NEP inhibitor of the formula (II-B) and one group was treated with ACE inhibitor ramipril.

Table 4: Urinary excretion of albumin and creatinin in GK rats, ramipril treated and rats treated with a compound of the formula (II-B) starting at an animal age of 6 month:

	Albumin/Creatinin mg/mmol		
	Basal	6 weeks treatment	12 weeks treatment
Placebo GK rats			
Mean	103,95	329,37	1183,19
s	71,42	230,17	637,71
SEM	20,62	66,44	184,09
N	12	12	12
Cpd. (II-B) GK rats			
Mean	103,95	17,70	24,28
s	71,42	6,01	14,41
SEM	20,62	1,74	4,16
N	12	12	12
Ramipril GK rats			
Mean	103,95	161,71	244,89
S	71,42	112,42	146,00
SEM	20,62	32,5	44,0
N	12	12	11

Example 3:

The albumin and creatinin excretion in Wistar rats was determined. One group was left untreated, one was treated with the ACE/NEP inhibitor of the formula (II-B) and one group was treated with ACE inhibitor ramipril. Wistar rats are non-diabetic and develop proteinuria and structural kidney damages during addult life. Wistar rats are therefore a model for non-diabetic nephropathy.

Figure 1 shows age-related non-diabetic nephropathy in placebo-teated Wistar rats (kidney of a placebo rat displaying moderate tubulo-interstilial lesions (proteineous casts in the tubules, inflammatory cell infiltration, basophilic tubules)).

Table 5: Urinary excretion of albumin and creatinin in Wistar rats, ramipril treated and rats treated with a compound of the fomula (II-B) starting at an animal age of 6 month:

	Albumin/Creatinin mg/mmol		
	Basal	6 weeks treatment	12 weeks treatment
Placebo Wistar rats			
Mean	130,45	149,82	290,10
S	285,53	231,12	265,69
SEM	90,29	64,10	73,69
N	10	13	13
Cpd. (II-B) Wistar rats			
Mean	130,45	18,07	21,21
S	285,53	17,64	29,49
SEM	90,29	4,89	8,18
N	10	13	13

Ramipril Wistar rats			
Mean	130,45	184,27	188,40
S	285,53	171,87	146,47
SEM	90,29	49,62	42,28
N	10	12	12

In the non-diabetic model, the compound of the formula (II-B) shows a significantly higher nepühroprotective effect than ramipril as determined by the extent of proteinuria.

AGE RELATED DISEASES

Incubation of proteins or lipids with aldose sugars results in nonenzymatic glycation and oxidation of amino groups on proteins to form Amadori adducts. Over time, the adducts undergo additional rearrangements, dehydrations, and cross-linking with other proteins to form complexes known as Advanced Glycosylation End Products (AGEs). The formation of AGEs can also be described as Maillard reactions. Factors which promote formation of AGEs included delayed protein turnover (e.g. as in amyloidoses), accumulation of macromolecules having high lysine content, and high blood glucose levels (e.g. as in diabetes) (Hori et al., J. Biol. Chem. 270: 25752-761, (1995)). AGEs have implicated in a variety of disorders including complications associated with diabetes and normal aging.

AGEs display specific and saturable binding to cell surface receptors on endothelial cells of the microvasculature, monocytes and macrophages, smooth muscle cells, mesengial cells, and neurons. The Receptor for Advanced Glycated Endproducts (RAGE) is a member of the immunoglobulin super family of cell surface molecules.

Increased levels of RAGE are found in aging tissues (Schleicher et al., J. Clin. Invest. 1997, 99, 457-468), and the diabetic retina, vasculature and kidney (Schmidt et al., Nature Med. 1995, 1002-1004). Activation of RAGE in different tissues and organs leads to a number of pathophysiological consequences. RAGE has been

implicated in a variety of conditions including: acute and chronic inflammation (Hofmann et al, Cell 1999, 97, 889-901), the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy by accumulation of AGEs in the kidneys and other tissues (Singh et al., Diabetologia 2001, 44, 129-146), as well as in Alzheimer's disease (Yan et al., Nature 1996, 382, 685-691), erectile dysfunction, tumor invasion and metastasis (Taguchi et al., Nature 2000, 405, 354-357).

The ACE inhibitor ramipril is known to influences the serum levels of advanced glycation endproducts in high risk patients with coronary artery disease: results from a HOPE study (B. Kihovd, E.M. Hjerkinn, I. Seljeflot, T.J. Berg, A.A. Reikvam)

It has now been found that compounds of the formula (I) significantly reduce the accumulation of AGEs in the kidneys and in the heart. Therefore, compounds of the formula (I) are useful for the prevention and/or treatment of metabolic diseases associated with advanced glycation end-products, especially diabetic complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, myocardial infarction, cataracts and diabetic cardiomyopathy.

Kidney AGE values were determined by Dot blot analysis (Stracke et al., Exp. Clin. Endocrinol. Diabets 2002, 109, 330-336) and Reversed-phase high performance liquid chromatography or RP-HPLC (Drusch et at., Food Chem. 1999, 65, 547-553).

Treatment of diabetic rats with a compound of the formula (II-B) normalizes the kidney AGE (CML) values, treatment with M100.240 lowers the CML value significantly.

Example 4: Dot blot analysis

Kidney-samples for the dot blot analysis were obtained from 17 week old male ZDF rats, control rats and ZDF rats treated for seven weeks with 30 mg/kg/d compound (II-B) and 35 mg/kg/d MDL 100.240. Three animals of each group were sacrificed, the kidneys removed and immediately frozen in liquid nitrogen. Grinding of the kidney was performed in liquid nitrogen using a freezer mill (Freezer 6750, C3

Analysetechnik GmbH). 10 mg kidney sample was dissolved in 1 ml phosphate buffered saline (PBS containing 0.5 g/l Tween 20, 0.5 mM PMSF, 1 µg/ml). The solution was treated two times for five seconds with an ultrasonic cell disrupter (45% power, Bandolin Sonoplus HD 2070), centrifuged for 20 minutes at 4000 rpm and the supernatant was used for dot blot analysis. The nitrocellulose membrane was placed in the dot blot apparatus and washed two times with 100 µl TBS/well. For each sample 10 µg protein (protein concentration of the samples were determined with the DC Protein Assay, Bio Rad) were diluted in 100 µl TBS and loaded on to the nitrocellulose membrane (Amersham). The membrane was incubated over night in TBST (20 mM Tris, 137 mM NaCl, 0.05% v/v Tween 20) with 5% non-fat dry milk at 4°C and incubated for 1 hour at room temperature using the following antibody concentration: anti-CML 011 (Biologo) 0.25 µg/ml, anti-CEL (Biologo) 0.25 µg/ml and anti-pentosidine 012 (Biologo) 0.25 µg/ml. After extensive washing in TBST with 5% non-fat dry milk, membranes were exposed to alkaline peroxidase-labeled anti-mouse IgG antibodies (Dianova) for one hour at room temperature. Membranes were washed again and exposed to the enhanced chemofluorescence detection system (Amersham) according to manufacturer's instructions. Relative fluorescence was determined with the Fluor-Imager 595 (Molecular Dynamics) and quantified using the Image-Quant software. Results were expressed in relative fluorescence (rf) times 10^5.

Table 6: Values of the AGE-subtype CML in the kidney of 17 week old ZDF rats, control rats and with compound (II-B) or MDL 100.240 treated ZDF rats.

kidneys of 17 week old rats anti-CML 011	n	mean rf * 10^5	SEM rf * 10^5	t-test	sign.
Lean control	3	32.20	1.22		
ZDF rats	3	45.14	3.23	0.0199	*
ZDF cpd. (II-B)	3	32.62	0.34	0.0182	*
ZDF MDL 100.240	3	38.67	1.38	0.1389	

Table 7: Values of the AGE-subtype CEL in the kidney of 17 week old ZDF rats, control rats and with a compound of the formula (II-B) or MDL 100.240 treated ZDF rats.

kidneys of 17 week old rats anti-CEL	n	mean rf * 10^5	SEM rf * 10^5
Lean control	3	54.49	2.55
ZDF rats	3	61.30	1.12
ZDF cpd. (II-B)	3	50.24	0.46
ZDF MDL 100.240	3	52.60	1.16

Table 8: Values of the AGE-subtype pentosidine in the kidney of 17 week old ZDF rats, control rats and with compound (II-B) or MDL 100.240 treated ZDF rats.

kidneys of 17 week old rats anti-pentosidine 012	n	mean rf * 10^5	SEM rf * 10^5
Lean control	3	52.78	1.65
ZDF rats	3	56.01	1.24
ZDF cpd. (II-B)	3	44.99	1.61
ZDF MDL 100.240	3	40.70	2.75

Values of the AGE-subtype CML are significant higher in kidneys of ZDF rats compared to the control rats (P<0.05). No significant difference between ZDF and control rats could be shown for the AGE-subtypes CEL and pentosidine. ZDF rats treated with a compound of the formula (II-B) show significant less AGE values for the AGE-subtype CML, CEL and pentosidine (P<0.05) compared to untreated ZDF rats. Lower AGE values for the subtypes CEL and pentosidine can also be determined in ZDF rats treated with MDL 100.240 (P<0.01).

Example 5: Reversed-phase high performance liquid chromatography (RP-HPLC)

Kidney- and heart-samples for the RP-HPLC analysis were obtained from 17 week old male ZDF rats, control rats and ZDF rats treated for seven weeks with 30 mg/kg/d compound of the formula (II-B) and 35 mg/kg/d MDL 100.240. Two animals of each group were analyzed. Grinding of the kidney and heart was performed in liquid nitrogen using a freezer mill (Freezer 6750, C3 Analysetechnik GmbH).
Hydrolysis of the organ samples was performed with 6 M hydrochloric acid (HCL) at

110 °C for 12 hours. Sample derivatisation with o-Phthaldialdehyde (OPA) and RP-HPLC was performed as described in Drusch et at., Food Chem. 1999, 65, 547-553.

Table 9: Values of the AGE-subtypes CML in the kidney of 17 week old ZDF rats, control rats and with a compound of the formula (II-B) or MDL 100.240 treated ZDF rats.

RP-HPLC kidneys 17 week old rats	n [animals]	mean CML conc. [%]	SEM [%]
ZDF Placebo	2	100	0.27
Lean control	2	84	1.19
Cpd. (II-B)	2	55	3.83
MDL 100.240	2	60	10.15

Table 10: Values of the AGE-subtypes CML in the kidney of 37 week old ZDF rats, control rats and with a compound of the formula (II-B) or MDL 100.240 treated ZDF rats. Values with P<0.05 were considered significant (*P<0.05; **P<0.01).

RP-HPLC kidneys 37 week old rats	n [animals]	mean CML conc. [%]	SEM [%]	t-test	sign.
ZDF Placebo	2	100	2.00	0.010	*
Lean control	2	79	0.17		
ZDF cpd. (II-B)	2	58	4.46	0.014	*
ZDF MDL 100.240	2	93	4.77	0.298	

Table 11: Values of the AGE-subtypes CML in the heart of 17 week old ZDF rats, control rats and with a compound of the formula (II-B) or MDL 100.240 treated ZDF rats. Values with P<0.05 were considered significant (*P<0.05; **P<0.01).

RP-HPLC hearts 17 week old rats	n [animals]	mean CML conc. [%]	SEM [%]	t-test	sign.
ZDF Placebo	2	100	3.74	0.015	*
Lean control	2	32	7.28		

ZDF cpd. (II-B)	2	26	10.95	0.025	*
ZDF MDL 100.240	2	66	3.29	0.022	*

ZDF rats show significant higher CML concentration in the kidney of 17 and 37 week old rats and the heart of 17 week old rats compared to control rats ($P<0.05$). Treatment with a compound of the formula (II-B) reduces the CML concentration in the kidney of 17 and 37 week old ZDF rats as well as the CML concentration in the heart of 17 week old ZDF rats. MDL 100.240 also reduces the CML concentration in kidney and heart of 17 week old ZDF rats, but not in the kidney of 37 week old ZDF rats.

INSULIN RESISTENCE

The compounds of the formula (I) also show insulin sensitizing activity. The prophylactic action of the compounds of the formula (I) upon nephropathy is also indicative that an insulin sensitising agent can be expected to prevent, reverse, stabilise or retard the progression of microalbuminuria to albuminuria. This is because microalbuminuria is considered to be a predictor of future nephropathy, especially in patients with clinical evidence of pre-diabetic insulin resistance syndrome, alternatively referred to as Syndrome X.

The use of ACE or vasopeptidase inhibitors for the treatment of insulin resistence has not been examined so far.

It has now been found that compounds of the formula (I) significantly lower blood glucose concentrations and HbA1c values and thereby reduce insulin resistense. HbA_{1c} is a measure for long-time glucose values. Glycated HbA_{1c} is an early AGE, a so-called Amadori product.

The effect of a compound of the formula (II-B) on HbA_{1c} and blood glucose value is similar to M100.240, and both compounds show lower values than ACE inhibitor ramipril.

Example 6: Blood glucose and HbA_{1c} analysis in ZDF rats

Blood glucose and HbA_{1c} was measured in ten and seventeen week old male Zucker diabetic fatty rats (Genetic Model Inc.), control rats (Genetic Model Inc.) and male ZDF rats treated for seven weeks with 30 mg/kg/d compound of the formula (II-B), 35 mg/kg/d MDL 100.240 and 1 mg/kg/d Ramipril. Fifteen animal were analyzed in each group.

Blood samples for glucose determination were obtained from ZDF rats using standard sampling tubes. Within 30 minutes of collection samples were separated from the cells by centrifugation. Quantitative determination of blood glucose in serum was performed with an enzymatic *in vitro* test from Roche Diagnostics GmbH (Gluco-quant, Roche Diagnostics GmbH) using the automated clinical chemistry analyzer Boehringer Mannheim/Hitachi 912.

To obtain blood samples for HbA_{1c} determination, disposable capillary tubes were used. HbA_{1c} values were obtained from hemolyzed whole blood samples with a turbidimetric inhibition immunoassay (Tina-quant, Roche Diagnostics GmbH) and hemoglobin concentrations were determined in a second channel on an automated clinical chemistry analyzer (Boehringer Mannheim/Hitachi 912). HbA_{1c} concentration in percent were calculated from HbA_{1c} to total hemoglobin.

Table 12: Blood glucose concentration in 10 and 17 week old ZDF rats, control rats and with compound (II-B), MDL 100.240 and Ramipril treated ZDF rats.

blood glucose	ZDF rats		control		ZDF Cpd. (II-B)		ZDF Ramipril		ZDF MDL100.240	
age [weeks]	10	17	10	17	10	17	10	17	10	17
mean [mM]	11.92	29.68	7.32	8.04	10.67	21.09	11.74	27.33	10.37	19.74
SEM [mM]	1.74	1.32	0.15	0.34	1.49	2.78	1.48	1.75	1.40	2.10
n [animals]	15	15	20	20	15	15	15	15	15	15

Table 13: HbA_{1c} values in 10 and 17 week old ZDF rats, control rats and with compound (II-B), MDL 100.240 and Ramipril treated ZDF rats.

HbA_{1c}	ZDF rats		control		ZDF Cpd. (II-B)		ZDF Ramipril		ZDF MDL100.240	
age [weeks]	10	17	10	17	10	17	10	17	10	17
mean [%]	6.14	9.96	4.49	4.62	5.69	8.24	5.66	9.48	5.60	7.19
SD [%]	0.22	0.42	0.02	0.02	0.16	0.71	0.14	0.52	0.15	0.46
n [animals]	15	15	20	20	14	15	15	15	15	15

Blood glucose concentration and HbA_{1c} values are significant lower in the control animals compared to the ZDF rats (P<0,01). The 17 weeks old male ZDF rats treated with MDL 100.240 or compound (II-B) show also significant lower blood glucose concentration and HbA_{1c} values compared to the untreated ZDF rats. No significant difference for blood glucose or HbA_{1c} can be shown in Ramipril treated 17 week old ZDF rats compared to the untreated ZDF rats.

ENDOTHELIAL DYSFUNCTION AND ATHEROSCLEROTIC PLAQUES

In the atherogenic rabbit model (White New Zealand rabbits were fed with 0.25% cholesterol plus 3% coconut oil) was shown, that even a short period with atherogenic diet of 6 weeks already leads to a sustained endothelial dysfunction, although thereafter the animals received for 3 months a normal diet. In all experiments yet known the animals were fed constantly during the whole time course fed with atherogenic diet and had un-physiologic extreme high cholesterol levels not comparable to the situation in humans.

The endothelial dysfunction as well as the atherogenic changes in the blood vessels were both prevented and reversed by treatment with the ACE/NEP inhibitor of the compound of the formula (II-B), first time investigated and shown in direct comparison to the ACE inhibitor, ramipril. As measure for the endothelial dysfunction served the endothelium-dependent relaxation on isolated aortic rings of the rabbits as well as the nitric oxide and superoxide release from the endothelial cells.

Example 7: Effects of long-term treatment with the ACE/NEP inhibitor of the compound of the formula (II-B) on endothelial dysfunction and atherosclerotic

plaques in rabbits fed with an atherogenic diet

Groups:

Standard : 18 weeks normal diet

Atherogenic : 18 weeks atherogenic diet (3% Coconut oil + 0,25% Cholesterol)

Varied diet (Var.) : 6 weeks atherogenic diet + 12 weeks normal diet

Varied Diet + Ramipril : 6 weeks atherogenic diet + 12 weeks normal diet + Ramipril

Varied diet + compound (II-B): 6 weeks atherogenic diet + 12 weeks normal diet + cpd. (II-B)

Table 14: Relaxation of aortic rings by acetylcholine (ACh) in 4 increased concentrations (10^{-8} mol/L, 10^{-7} mol/L, 10^{-6} mol/L and 10^{-5} mol/L) after preceding stimulation by phenylephrine (10^{-7} mol/L) (data in %; $\bar{x}$ ± SEM)

ACh Groups	10^{-8} mol/L	10^{-7} mol/L	10^{-6} mol/L	10^{-5} mol/L
Normal Diet	11,65 ± 1,55	52,68 ± 3,06	75,64 ± 2,83	83,81 ± 3,3
Atherogenic Diet	2,18 ± 1,23	7,07 ± 2,76 * # ° †	11,82 ± 3,88 * # ° †	12,49 ± 4,1 * # ° †
Var. Diet	10,76 ± 2,29	43,33 ± 3,57 †	63,48 ± 2,89 † # °	69,41 ± 2,82 † # °
Var. + Ramipril	13,08 ± 2,22	51,86 ± 4,43	77,34 ± 3,7	83,73 ± 4,03
Var. + cpd. (II-B)	19,9 ± 3,48	59,62 ± 6,43	76,4 ± 6,38	80,89 ± 6,82

*: $p<0,05$ vs. Varied diet;

#: $p<0,05$ vs. Normal diet;

°: $p<0,05$ vs. Var.+ Ram.

†: $p<0,05$ vs. Var.+ cpd. (II-B)

Table 15: NO- and Superoxide (O_2^-) data (in nmol/L; $\bar{x}$ ± SEM)

Groups	NO (nM)	O_2^- (nM)
Normal Diet	306,71 ± 36,16 *	29,41 ± 5,89
Atherogenic D.	167,77 ± 30,65	52,12 ± 7,06 #
Var. Diet	174,39 ± 25,44	35,86 ± 7,49

Var. +Ramipril	368,31 ± 42,25 *	48,09 ± 7,91 #
Var. + cpd. (II-B)	329,19± 30,10 *	30,18 ± 6,00

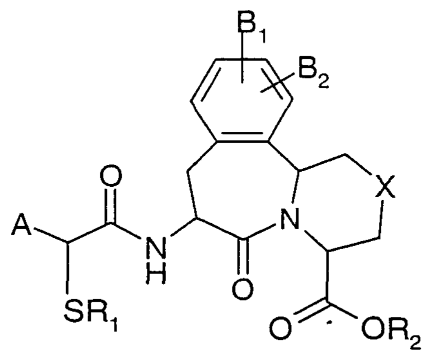
*: p<0,05 vs. Varied diet, vs. atherogenic diet;

#: p<0,05 vs. Varied diet ,vs. Normal diet, vs. Varied diet + cpd. (II-B))

NO and O_2^- are markers for endothelial function: increased relaxation and NO-levels are beneficial, while increased O_2^- formation inhihibts the beneficial effects of NO.

Claims:

1. Use of a compound of formula (I)



(I)

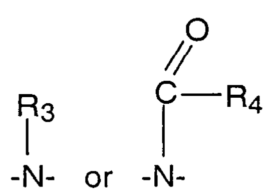
wherein

A = H, C_1-C_8-alkyl, $CH_2OCH_2CH_2OCH_3$, -(C_1-C_4-alkyl)-aryl;

R_1 is hydrogen, -$CH_2OC(O)C(CH_3)_3$, or an acyl group;

R_2 is hydrogen; -CH_2O-$C(O)C(CH_3)_3$; a C_1-C_4-alkyl; aryl, -(C_1-C_4-alkyl)-aryl; or diphenylmethyl;

X is –$(CH_2)_n$ wherein n is an integer 0 or 1, -S- , –O- ,



wherein R_3 is hydrogen, a C_1-C_4-alkyl, aryl or aryl-(C_1-C_4-alkyl) and R_4 is –CF_3, C_1-C_{10}-alkyl, aryl, or aryl-(C_1-C_4-alkyl);

B_1 and B_2 are each independently hydrogen, hydroxy, -OR_5, wherein R_5 is C_1-C_4-alkyl, aryl, or -(C_1-C_4-alkyl)-aryl or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbon atoms to form a benzene ring or methylenedioxy,

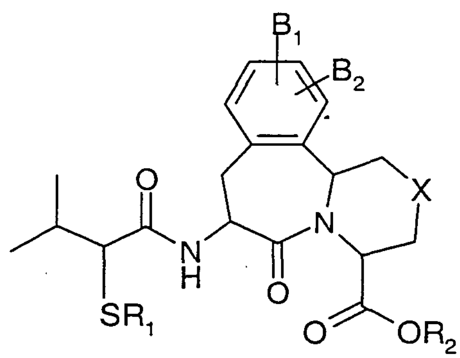
for the treatment and/or prophylaxis of nephropathy in diabetic patients or

for the treatment and/or prophylaxis of non-diabetic patients, or

for the treatment and/or prophylaxis of insulin resistence or metabolic diseases associated with advanced glycation end-products, or

for the treatment and/or prophylaxis of atherosclerosis or endothelial dysfunction.

2. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (II)



(II)

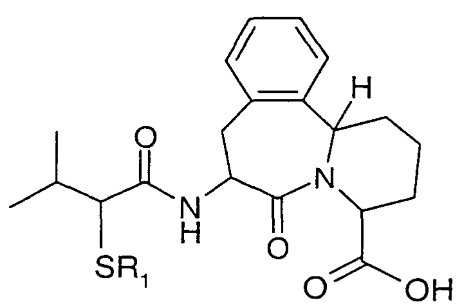
and R_1 is acetyl.

3. Use according to claim 2, wherein R_1 is hydrogen.

4. Use according to claim 2, wherein B_1 and/or B_2 are hydrogen.

5. Use according to claim 2, wherein X is $-CH_2$.

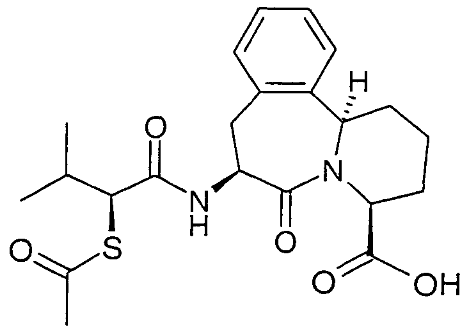
6. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (II-A):



(II-A)

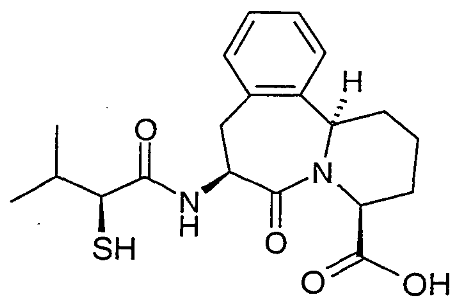
wherein R_1 is acetyl or hydrogen.

7. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (II-B)



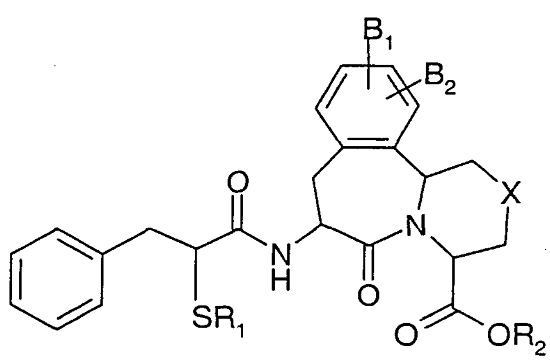
(II-B)

8. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (II-C)



(II-C)

9. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (III)



(III)

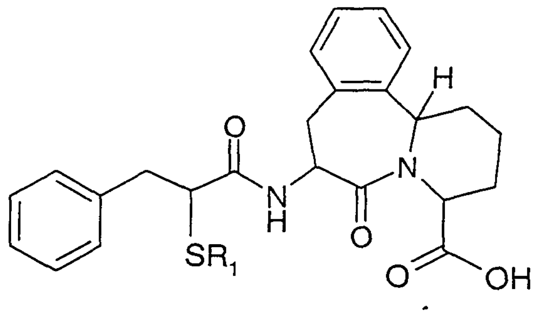
and R_1 is acetyl.

10. Use according to claim 9, wherein R_1 is hydrogen.

11. Use according to claim 9, wherein B_1 and/or B_2 are hydrogen.

12. Use according to claim 9, wherein X is $-CH_2$.

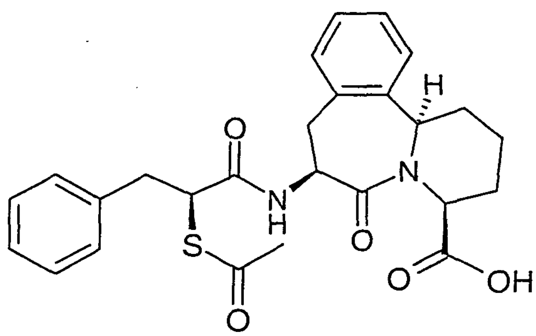
13. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (III-A):



(III-A)

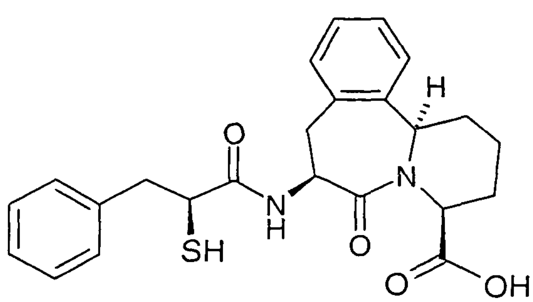
wherein R_1 is acetyl or hydrogen.

14. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (III-B)



(III-B)

15. Use according to claim 1, wherein the compound of the formula (I) is characterized by a compound of the formula (III-C)

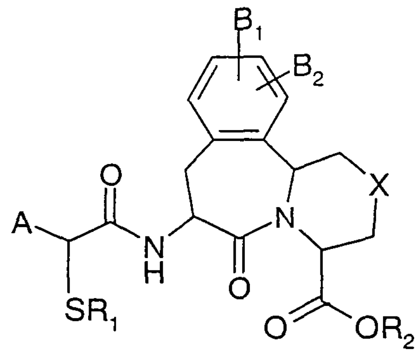


(III-C)

DEAV2002/0044

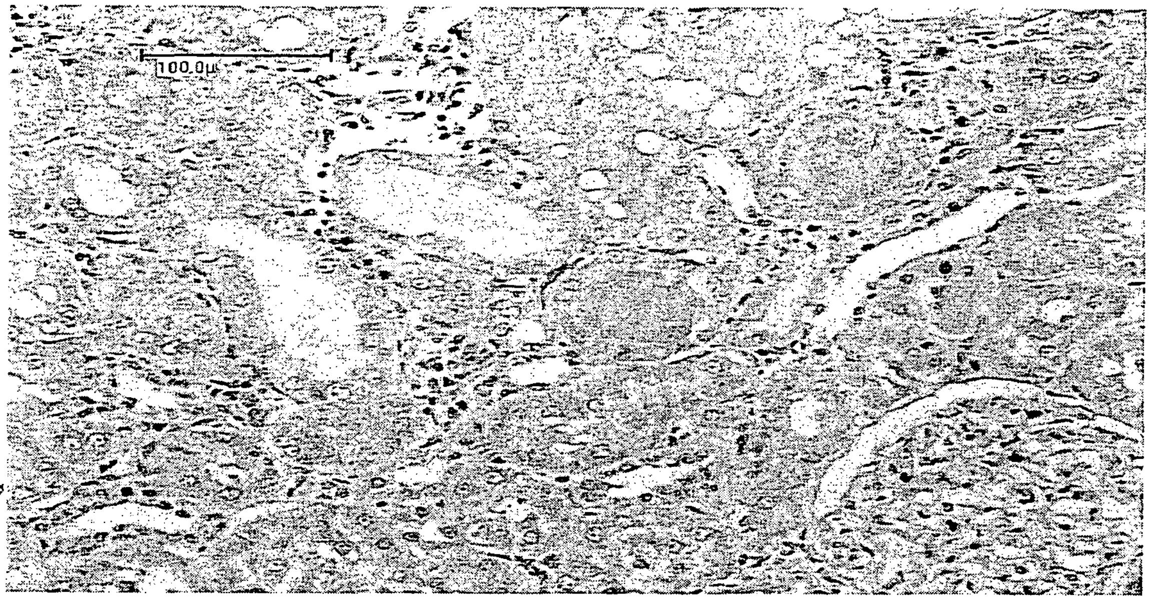
Abstract

The invention describes the use of vasopeptidase inhibitors of the formula (I)


(I)

for the treatment and/or prophylaxis of nephropathy in diabetic or non-diabetic patients, including diabetic or non-diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndome, hypertensive nephrosclerosis, microalbuminuria or end stage renal disease, or insulin resistence or of metabolic diseases associated with advanced glycation end-products, such as diabetic complications, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, myocardial infarction and/or diabetic cardiomyopathy, or atherosclerosis or endothelial dysfunction.

Figure 1:



Kidney of a placebo rat displaying moderate tubulo-interstilial lesions (proteineous casts in the tubules, inflammatory cell infiltration, basophilic tubules;, orig. magn. x 100